15. (Amended) The pharmaceutical composition of claim 13 further comprising a facilitator.

17. (Amended) A method of inducing an immune response against hepatitis C virus in a human uninfected by hepatitis C virus comprising administering to said human a recombinant nucleic acid molecule comprising a nucleotide sequence encoding a hepatitis C virus nonstructural protein in an amount effective to induce an immune response against hepatitis C virus.

32. (Amended) A method of treating a human who is infected with hepatitis C virus comprising administering to said human a pharmaceutical composition of claim 13 in an amount effective to induce a therapeutic immune response against hepatitis C virus.

REMARKS

Claims 1-33 are pending in the present application. Claims 1, 5, 9 and 29-31 have been canceled without prejudice to their presentation in another application. Claims 2-4, 6, 8, 10-13, 15, 17 and 32 have been amended, support for which can be found in the claims and throughout the specification. Upon entry of the present amendment, claims 2-4, 6-8, 10-28, 32 and 33 will be pending.

Applicants thank the Examiner for pointing out and correcting the error in numbering the claims. In addition, Applicants have added new page 28 of the specification containing the Abstract. The Abstract is identical to the Abstract that was filed in International Application No. PCT/US99/01823, of which the present application is the national phase. In addition, the specification has been amended to correct the typographical errors as suggested at page 2 of the Office Action.

I. The Claimed Invention Is Novel

A. The Selby Reference

Claims 1, 2, 4 and 8 stand rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Selby *et al.*, *J. Gen. Virol.*, **1993**, *74*, 1103-1113 (hereinafter, the "Selby reference"). Applicants

traverse the rejection and respectfully request reconsideration because the Selby reference does not teach every feature recited in claim 6 and claims dependent thereon.

Claim 6 has been amended to incorporate the subject matter of claim 1, which has been cancelled. Claims 2, 4 and 8 have been amended to be dependent on claim 6. Claim 6 has not been rejected as being anticipated by the Selby reference. Indeed, the Selby reference does not teach a recombinant nucleic acid molecule comprising a nucleotide sequence encoding a hepatitis C virus nonstructural protein wherein the nucleotide sequence is operably linked to a promoter, enhancer, polyadenylation sequence, and optionally 5' UTR of hepatitis C virus. Thus, the Selby reference does not teach every feature recited in claim 6 and claims 2, 4, and 8, which are dependent thereon. Accordingly, Applicants respectfully request that the rejection of claims 1, 2, 4 and 8 under 35 U.S.C. §102(b) be withdrawn.

B. The D'Souza Reference

Claims 1-4 stand rejected under 35 U.S.C. §102(b) as allegedly being anticipated by D'Souza *et al.*, *J. Gen. Virol.*, **1995**, *76*, 1729-1736 (hereinafter, the "D'Souza reference"). Applicants traverse the rejection and respectfully request reconsideration because the D'Souza reference does not teach every feature recited in claim 6 and claims dependent thereon.

Claim 6 has been amended to incorporate the subject matter of claim 1, which has been cancelled. Claims 2-4 have been amended to be dependent on claim 6. Claim 6 has not been rejected as being anticipated by the D'Souza reference. Indeed, the D'Souza reference does not teach a recombinant nucleic acid molecule comprising a nucleotide sequence encoding a hepatitis C virus nonstructural protein wherein the nucleotide sequence is operably linked to a promoter, enhancer, polyadenylation sequence, and optionally 5' UTR of hepatitis C virus. Thus, the D'Souza reference does not teach every feature recited in claim 6 and claims 2-4, which are dependent thereon. Accordingly, Applicants respectfully request that the rejection of claims 1-4 under 35 U.S.C. §102(b) be withdrawn.

C. The Harada Reference

Claims 1, 2, 4, 5 and 8 stand rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Harada *et al.*, *J. Gen. Virol.*, **1995**, *76*, 1215-1221 (hereinafter, the "Harada reference"). Applicants traverse the rejection and respectfully request reconsideration because the Harada reference does not teach every feature recited in claim 6 and claims dependent thereon.

Claim 6 has been amended to incorporate the subject matter of claim 1, which has been cancelled. Claim 5 has been canceled. Claims 2, 4 and 8 have been amended to be dependent on claim 6. Claim 6 has not been rejected as being anticipated by the Harada reference. Indeed, the Harada reference does not teach a recombinant nucleic acid molecule comprising a nucleotide sequence encoding a hepatitis C virus nonstructural protein wherein the nucleotide sequence is operably linked to a promoter, enhancer, polyadenylation sequence, and optionally 5' UTR of hepatitis C virus. Thus, the Harada reference does not teach every feature recited in claim 6 and claims 2, 4 and 8, which are dependent thereon. Accordingly, Applicants respectfully request that the rejection of claims 1, 2, 4, 5 and 8 under 35 U.S.C. §102(b) be withdrawn.

II. The Claimed Invention Is Not Obvious

A. The Combination Of The Selby and Selden References

Claims 9-13 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over the Selby reference in view of Selden, *Curr. Prot. Mol. Biol.*, **1987**, 9.2.1 (hereinafter, the "Selden reference"). The Office Action mistakenly asserts that it would have been *prima facie* obvious for one skilled in the art to have resuspended the nucleic acid molecule of the Selby reference in tris buffered saline of the Selden reference. Applicants traverse the rejection and respectfully request reconsideration because even if the Selby and Selden references are combined, the claimed invention would not be produced.

Claim 13 has been amended to incorporate the subject matter of claim 9, which has been cancelled. Claims 10-12 have been amended to be dependent on claim 13. Claim 13 has been mistakenly rejected as being obvious over the combination of the Selby and Selden references. As stated above, the Selby reference does not teach a recombinant nucleic acid molecule comprising a

nucleotide sequence encoding a hepatitis C virus nonstructural protein wherein the nucleotide sequence is operably linked to a promoter, enhancer, polyadenylation sequence, and optionally 5' UTR of hepatitis C virus, as is recited in claim 13. Indeed, claim 6 was not rejected over the Selby reference. Further, the Selden reference does not teach, nor is it alleged in the Office Action, a recombinant nucleic acid molecule comprising a nucleotide sequence encoding a hepatitis C virus nonstructural protein wherein the nucleotide sequence is operably linked to a promoter, enhancer, polyadenylation sequence, and optionally 5' UTR of hepatitis C virus. Thus, the Selden reference does not cure the deficiencies of the Selby reference. Thus, the combination of the Selby and Selden references does not teach every feature recited in claim 13 and claims 10-12, which are dependent thereon. Accordingly, Applicants respectfully request that the rejection of claims 9-13 under 35 U.S.C. §102(b) be withdrawn.

B. The Selby Reference

Claims 7, 8 and 14 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over the Selby reference. The Office Action mistakenly asserts that it would have been *prima facie* obvious for one skilled in the art to combine the nucleic acid molecule of the Selby reference with the CMV promoter and Rous sarcoma virus enhancer to modulate expression. Applicants traverse the rejection and respectfully request reconsideration because there is no motivation to modify the nucleic acid molecule of the Selby reference.

In establishing a *prima facie* case of obviousness under 35 U.S.C. §103, it is incumbent upon the Examiner to provide a reason why one of ordinary skill in the art would have been led to modify a prior art reference or to combine reference teachings to arrive at the claimed invention. *Ex parte Clapp*, 227 U.S.P.Q. 972 (Bd. Pat. App. Int. 1985). To this end, the requisite motivation must stem from some teaching, suggestion or inference in the prior art as a whole or from the knowledge generally available to one of ordinary skill in the art and not from appellants' disclosure, see for example, *Uniroyal Inc. v. Rudkin-Wiley Corp.*, 5 U.S.P.Q.2d 1434 (Fed. Cir. 1988); and *Ex parte Nesbit*, 25 U.S.P.Q.2d 1817, 1819 (Bd. Pat. App. Int. 1992). In this respect, the following quotation from *Ex parte Levengood*, 28 U.S.P.Q.2d 1300, 1302 (Pat. Off. Bd. App. 1993), is noteworthy:

> Our reviewing courts have often advised the Patent and Trademark Office that it can satisfy the burden of establishing a *prima facie* case of obviousness only by showing some objective teaching in either the prior art, or knowledge generally available to one of ordinary skill in the art, that "would lead" that individual "to combine the relevant teachings of the references." ... Accordingly, an examiner cannot establish obviousness by locating references which describe various aspects of a patent applicant's invention without also providing evidence of the motivating force that would **impel** one skilled in the art to do what the patent applicant has done. (citations omitted; emphasis added)

Significantly, the Office Action identifies no "motivating force" that would "impel" persons of ordinary skill to modify the respective teachings of the cited references and achieve the claimed invention. The only motivation for combining the references in the manner identified in the Office Action is that the CMV promoter and Rous sarcoma virus enhancer are known and have been used to express proteins and that it is routine to use such elements. This alleged motivation, however, in no way would lead one skilled in the art to modify the teachings of the Selby reference to arrive at Applicants' claimed inventions.

The only motivation alleged by the Examiner is to modulate the expression level of the protein. The Selby reference, however, does not teach that expression levels should be further modulated. Indeed, authors of the Selby reference replaced the entire 5' UTR of HCV with β-globin or EMCV leader sequences to obtain better expression. There is no teaching or suggestion in the Selby reference that the constructs described therein, which contain the β-globin or EMCV leader sequences, were in any way inadequate in protein expression. Thus, one skilled in the art would not have been motivated to modulate the expression of the nucleic acid molecules reported in the Selby reference, let alone modify them by inserting either or both of the CMV promoter or Rous sarcoma virus enhancer. The alleged motivation is, at best, an invitation for further experimentation and, at most, provides an "obvious to try" situation. However, "obvious to try" is not the standard of 35 U.S.C. §103. *In re Geiger*, 2 U.S.P.Q.2d 1276, 1278 (Fed. Cir. 1987). Applicants further note that "[i]t is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious." *In re Fritch*,

23 U.S.P.Q.2d 1780, 1784 (Fed. Cir. 1992). Under this standard, the Selby reference neither discloses nor suggests the claimed inventions. Accordingly, Applicants respectfully request that the rejection of claims 7, 8 and 14 under 35 U.S.C. §103(a) be withdrawn.

III. The Claimed Invention Is Sufficiently Enabled

Claims 9-33 stand rejected under 35 U.S.C. §112, first paragraph as allegedly failing to provide an enabling disclosure. The Office Action mistakenly asserts that it would require undue experimentation for one skilled in the art to practice the claimed invention. Applicants traverse the rejection and respectfully request reconsideration because one skilled in the art would be able to practice the claimed invention without being required to perform undue experimentation.

As will be recognized, the enablement requirement of §112 is satisfied so long as a disclosure contains sufficient information that persons of ordinary skill in the art having the disclosure before them would be able to make and use the invention. *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988) (the legal standard for enablement under §112 is whether one skilled in the art would be able to practice the invention without undue experimentation). In this respect, the following statement from *In re Marzocchi*, 169 U.S.P.Q. 367, 369-370 (C.C.P.A. 1971), is noteworthy:

> The only relevant concern of the Patent Office under these circumstances should be over the truth of any such assertion. The first paragraph of §112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.
>
> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented **must** be taken as in compliance with the enabling requirements of the first paragraph of §112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied upon for enabling support. (emphasis added)

Any assertion by the Patent Office that an enabling disclosure is not commensurate in scope with the protection sought must be supported by evidence or reasoning substantiating the doubts so expressed. *In re Dinh-Nguyen*, 181 U.S.P.Q. 46 (C.C.P.A. 1974); *In re Bowen*, 181 U.S.P.Q. 48 (C.C.P.A. 1974).

The Office Action mistakenly asserts that it would require undue experimentation for one skilled in the art to use the pharmaceutical compositions recited in claims 9-16 to generate prophylactic or therapeutic immunity in humans. The Office Action mistakenly asserts that while Applicants demonstrate that the claimed pharmaceutical compositions elicit humoral, cytotoxic, and anti-tumor effects in mice (*see*, Figures 2, 3 and 4 of the specification), such data cannot be extrapolated to humans because mice are not a good model for HCV infections. The Office Action further asserts that "showing that the an [sic] immune response can be elicited in mice" does not mean that the nucleic acid molecule is sufficient to "provide humans with a prophylactic or therapeutic immunity." *See,* page 4 of the Office Action. Whether or not mice are a good model for HCV infections is irrelevant. What the Office Action appears to suggest is that in order to be enabled, Applicants' claimed invention must provide total immunity or cure an HCV infection. *In contrast, the claimed pharmaceutical compositions need only elicit an immune response.* Any immune response elicited in a human would be beneficial. Since the Office Action acknowledges that an immune response is generated in mice and offers no evidence that an immune response would not also be generated in humans, the claimed invention is sufficiently enabled. Indeed, there is no reason to believe that Applicants' claimed pharmaceutical compositions would not elicit an immune response in humans. Thus, claims 9-16 are sufficiently enabled.

The Office Action also mistakenly asserts that one skilled in the art would be required to perform undue experimentation to induce an immune response in humans, immunize a human, or treat a human infected with HCV, as recited in claims 17-33. The Office Action asserts that Applicants' specification teaches that the administration of the recombinant nucleic acid molecules can be used to "prophylactically and/or therapeutically immunize or treat an individual against HCV." Applicants do not disagree with this statement. The Office Action further acknowledges that any amount of DNA administered to a human might induce an immune response. Applicants also

do not disagree with this statement. The Office Action, however, incorrectly concludes that Applicants' recombinant nucleic acid molecules must provide protective immunity. Nothing of the sort, however, is required.

Claims 17-28 are directed to methods of inducing an immune response against HCV in a human. Claim 17 has been amended to incorporate the subject matter of cancelled claim 1. The Office Action already has acknowledged that Applicants' claimed compounds might, in fact, induce an immune response in humans. Indeed, Applicants have provided overwhelming evidence in the specification teaching that the claimed compounds elicit humoral, cytotoxic, and anti-tumor responses in mice. The Office Action has failed to provide any evidence whatsoever that would lead one skilled in the art to doubt that an immune response cannot be generated in humans, which is all that claims 17-28 recite. Thus, claims 17-28 are sufficiently enabled.

In regard to claims 29-31, which are directed to methods of immunizing a human susceptible to HCV, the Office Action asserts that the claims are, in essence, redundant to claims 17 and 23 [sic]. Applicants have cancelled claims 29-31 in view of pending claims 17-28. No change in the scope of the claimed inventions, however, is intended.

Claims 32 and 33, which are directed to methods of treating a human who is infected with HCV, are mistakenly asserted in the Office Action to lack enablement because Applicants allegedly fail to show that an immune response is sufficient to decrease the effects of a viral infection. Applicants respectfully point out that the Office Action has already acknowledged that Applicants claimed compounds and pharmaceutical compositions comprising the same generate humoral, cytotoxic, and anti-tumor responses in mice. The Office Action has also failed to provide any evidence whatsoever that would lead one skilled in the art to doubt that an immune response cannot be generated in humans. Further, the Office Action fails to provide any evidence that immune responses generated in a human would not decrease the effects of a viral infection. Indeed, any immune response generated against HCV in a human, as a matter of logic, results in a decrease in the HCV infection compared to generation of no immune response. Any immune response generated would be beneficial to the human receiving the immunization. Indeed, Applicants are not claiming a method of "curing" a disease. Thus, claims 32 and 33 are sufficiently enabled. Claims 32 and 33

have been amended to delete redundant material -- which is unrelated to the patentability of claims 32 and 33.

In view of the foregoing, there is no reason to believe that one skilled in the art would be required to perform undue experimentation in order to make and use the claimed invention. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph be withdrawn.

IV. Conclusion

In view of the foregoing, Applicants respectfully submit that the claims are in condition for allowance. An early notice of the same is earnestly solicited. The Examiner is invited to contact Applicants' undersigned representative at (215) 564-8906 if there are any questions regarding Applicants' claimed inventions. Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned **"Version with markings to show changes made."**

Respectfully submitted,

Paul K. Legaard
Registration No. **38,534**

Date: **May 8, 2001**

WOODCOCK WASHBURN KURTZ
MACKIEWICZ & NORRIS LLP
One Liberty Place - 46th Floor
Philadelphia, PA 19103
Telephone: (215) 568-3100
Facsimile: (215) 568-3439

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

The following paragraph has been inserted into the specification at page 1, line 3:

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application claims benefit of international application No. PCT/US99/01823 filed on January 28, 1999, which was published under PCT Article 21(2) in English, which claims priority to Serial No. 60/073,156 filed January 30, 1998, each of which is incorporated herein by reference in its entirety.

Paragraph beginning at page 9, line 12 of the specification has been amended as follows:

--When taken up by a cell, the gene constructs of the invention may remain present in the cell as a functioning extrachromosomal molecule or it may integrate into the cell's chromosomal DNA. Nucleic acid, such as DNA, may be introduced into cells where it remains as separate genetic material in the form of a plasmid. Alternatively, linear nucleic acid that can integrate into the chromosome may be introduced into the cell. When introducing nucleic acid into the cell, reagents which promote nucleic acid integration into chromosomes may be added. DNA sequences which are useful to promote integration may also be included in the DNA molecule. Alternatively, RNA may be administered to the cell. It is also contemplated to provide the gene construct as a linear minichromosome including a centromere, telomeres and an origin of replication.--

Paragraph beginning at page 9, line 22 of the specification has been amended as follows:

--According to the present invention, the gene construct comprises recombinant nucleic acid molecules comprising a nucleotide coding sequence that encodes a HCV nonstructural protein. In some preferred embodiments, the recombinant nucleic acid molecule comprises a nucleotide coding sequence that encodes NS3. In other preferred embodiments, the recombinant nucleic acid molecule comprises a nucleotide coding sequence that encodes a HCV nonstructural protein that comprises NS4. In other preferred embodiments, the recombinant nucleic acid molecule comprises a nucleotide coding sequence that encodes a HCV nonstructural protein that comprises NS5. In other preferred

embodiments, the recombinant nucleic acid molecule comprises a nucleotide coding sequence that encodes [a] any combination of HCV nonstructural proteins including NS3, NS4, and NS5.--

Paragraph beginning at page 17, line 22 of the specification has been amended as follows:

--The plasmid constructs were sequenced across the gene inserts and protein expression was certified in vitro in HuH-7 cells after transient transfection and in SP2/0 target cells after stable transfection, respectively. Protein [bans] bands of about 70 kD for NS3, 30 kD for NS4 and 125 kD for NS5 were found to be expressed within the cell but not secreted into the culture medium (see Figure 1B).--

The following paragraph has been inserted at new page 28 of the specification:

-- **ABSTRACT**

Nucleic acid molecule that comprise a hepatitis C nonstructural protein including specifically disclosed DNA sequences are disclosed. Pharmaceutical compositions that contain nucleic acid molecules comprising a hepatitis C nonstructural protein including a nucleotide sequence encoding NS3, NS4, or NS5, or a combination thereof, operably linked to regulatory elements functional in human cells are disclosed. Methods of immunizing individuals susceptible to or infected by hepatitis C virus comprising administering such pharmaceutical compositions are disclosed.--

In the Claims:

Claims 1, 5, 9 and 29-31 have been cancelled.

Claims 2-4, 6, 8, 10-13, 15, 17 and 32 have been amended as follows:

2. (Amended) The recombinant nucleic acid molecule of [claim 1] claim 6 wherein said nonstructural protein is selected from the group consisting of NS3, NS4, and NS5.

3. (Amended) The recombinant nucleic acid molecule of [claim 1] claim 6 wherein said nucleotide sequence encodes a fusion protein encoding NS3, NS4, or NS5, or any combination thereof.

4. (Amended) The recombinant nucleic acid molecule of [claim 1] claim 6 wherein said nucleotide sequence encodes a fragment of at least 50 amino acids of nonstructural protein selected from the group consisting of NS3, NS4, and NS5.

6. (Amended) A recombinant nucleic acid molecule comprising a nucleotide sequence encoding a hepatitis C virus nonstructural protein [The recombinant nucleic acid molecule of claim 5] wherein said nucleotide sequence is operably linked to a promoter, enhancer, polyadenylation sequence, and optionally 5' UTR of hepatitis C virus.

8. (Amended) A recombinant host cell comprising a nucleic acid molecule of [claim 1] claim 6.

10. (Amended) The pharmaceutical composition of [claim 9] claim 13 wherein said nucleotide sequence encodes a nonstructural protein selected from the group consisting of NS3, NS4, and NS5.

11. (Amended) The pharmaceutical composition of [claim 9] claim 13 wherein said nucleotide sequence encodes a fusion protein encoding NS3, NS4, or NS5, or any combination thereof.

12. (Amended) The pharmaceutical composition of [claim 9] claim 13 wherein said nucleotide sequence encodes a fragment of at least 50 amino acids of nonstructural protein selected from the group consisting of NS3, NS4, and NS5.

13. (Amended) A pharmaceutical composition comprising:

a) a recombinant nucleic acid molecule comprising a nucleotide sequence encoding a hepatitis C virus nonstructural protein, wherein said nucleotide sequence is operably linked to regulatory elements functional in human cells; and

b) a pharmaceutically acceptable carrier or diluent; [The pharmaceutical composition of claim 10]

wherein said regulatory elements functional in human cells comprise a promoter, enhancer, polyadenylation sequence, and optionally 5' UTR of hepatitis C virus.

15. (Amended) The pharmaceutical composition of [claim 9] claim 13 further comprising a facilitator.

17. (Amended) A method of inducing an immune response against hepatitis C virus in a human uninfected by hepatitis C virus comprising administering to said human [an amount of at least one] a recombinant nucleic acid molecule [of claim 1] comprising a nucleotide sequence encoding a hepatitis C virus nonstructural protein in an amount effective to induce an immune response against hepatitis C virus.

32. (Amended) A method of treating a human who is infected with hepatitis C virus comprising administering to said human [an amount of] a pharmaceutical composition of [claim 9] claim 13 in an amount effective to induce a therapeutic immune response against hepatitis C virus.